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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,306	06/05/2002	Antonino Cattaneo	LLG/2006.01/US	9842

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,306	CATTANEO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,11-16,19 and 38-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,11-16,19 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 5/30/06.

Claims 3-7, 9, 17, and were canceled and claims 38-45 were added as requested.

Claims 1, 8, 11-16, 19, and 38-45 are pending and under consideration in this Office Action.

Rejections Withdrawn

Applicant's submission of a certified translation of MI99A001783, filed 8/6/99, was sufficient to overcome the 102 rejections over Ruberti et al (2000), Capsoni et al (2/2000) and Capsoni et al (2000).

Applicant's amendments and the declaration of Dr Cattaneo were sufficient to overcome the rejections under 35 USC 112, first and second paragraphs. Note that new grounds of rejection under these statutes are set forth below.

Specification

The amendment filed 5/30/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

At the paragraph bridging pages 3 and 4 of the response, the specification is amended to include:

> "(F) Levels of mRNA for the VH-□D11 chain (left panel) and the VK-□D11 chain (right panel) in heart at P1 and P90 of mice from family 1, evaluated by phosphorimaging analysis, normalized to the □-actin mRNA (mean counts ± SEM). Number of mice for each age, n = 6."

The phrases "evaluated by phosphorimaging analysis, normalized to the □-actin mRNA (mean counts ± SEM)" and "Number of mice for each age, n = 6" represent new matter because there is no apparent support for these statements in the either the drawings or specification as filed.

At page 5 of the response, Applicant directs insertion into the specification of the following:

> "All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference."

This results in the introduction of new matter into the specification, because there was no indication in the specification as filed that any of the publications cited in therein, e.g. those listed at page 50, was intended to be incorporated by reference. Subsequent incorporation by reference introduces new matter into the disclosure. See 37 CFR 1.57.

Compliance with Sequence Rules

Applicant's amendments were sufficient to place the application in compliance with the requirements of 37 C.F.R.1.821-1.825.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 11-16, 19, and 38-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 11-16, 19, and 38-45 are indefinite because it is unclear what is intended by the phrase "an adult neurodegenerative pathology characterized by" the recited symptoms. Specifically, it is unclear if the phrase "characterized by" means that each of the recited symptoms must be evident in the claimed mouse, or only that the mouse must have a neuromuscular disorder in which each of the recited symptoms has been detected in the past, but not necessarily simultaneously. In other words, it is unclear if "characterized by" means that the recited symptoms are characteristic of the pathology, but necessarily present in each case, or whether each symptom must be present in each case of the pathology. So, it is unclear if the claim reads on an adult mouse with the recited transgenes that displays less than all of the recited symptoms, or whether the adult mouse must express, or be predisposed to expressing, each and every one of the recited symptoms. This rejection could be overcome by deleting ", an adult neurodegenerative pathology characterized by the presence of:".

These claims are also indefinite in their recitation of "behavioral cognitive deficit". This term is not defined in the specification and is not a term of art (a Medline search returned 0 hits). As a result, one of skill in the art cannot know the metes and bounds of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1, 8, 11-16, 19 and 38-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 8, 11-16, and 38-45 have been amended to require that the transgenic mouse has "behavioral cognitive deficit". At page 11 of the response, Applicant indicates that this term is supported at pages 7-1, Examples 2, and 3, and in the originally filed claims. However, after reviewing these passages, the Examiner failed to find support for this term. Furthermore, as discussed above, it is not a term of the art, and its metes and bounds are unclear. As a result, the amendment introduces new matter.

Claims 14-16 depend from claim 38. claim 38 requires a transgenic mouse that produces a fully constituted anti-NGF antibody at a level of at least 50 ng/ml by postnatal day 45. Applicant asserts that this claim is supported b the specification as a whole, the claims as filed, and Examples 1 and 3. However, after reviewing the originally filed claims, Examples 1 and 3, and the specification, the Examiner failed to

find support for this combination of limitations, particularly "a level of at least 50 ng/ml by postnatal day 45", so it represents new matter.

New claims 44 and 45 are drawn to urine, and to cerebrospinal fluid, respectively, from a transgenic mouse. The claims broadly embraces isolated urine and cerebrospinal fluid. At page 12 of the specification, applicant asserts that support for these claims is provided by disclosure of the mouse of claim 1, and asserts that the working examples describe the isolation of urine and cerebrospinal fluid. Applicant did not specifically point to any page or line of the specification providing support for this amendment. No such support is readily apparent, so the claims represent new matter.

Scope of Enablement

Claims 1, 8, 12, 13, 19, and 38-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse that expresses transgenes encoding the heavy and light chains of an antibody that is specific for NGF, wherein the expressed gene products combine to form an antibody or fragment thereof that is specific for NGF and prevents binding of NGF to its receptors, wherein the mouse has one or more of the following phenotypic characteristics: deposition in the central nervous system of plaques of amyloid precursor protein or beta amyloid protein, hyperphosphorylation of tau protein, neurofibrillary tangles, cortical atrophy, hippocampal atrophy, cerebral ventricle dilation, reduced number of forebrain cholinergic neurons, glial activation, skeletal muscle atrophy, amyloid precursor protein deposits in skeletal muscles, skeletal muscle inflammation, skeletal muscle

vacuolization, and a spatial learning deficit, does not reasonably provide enablement for mice that express an anti-NGF antibody that cross reacts with other neurotrophins such as NT-3 or BDNF, or that express an antibody specific for NGF that does not inhibit NGF binding to its receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1 is directed to a transgenic mouse comprising transgenes encoding a variable heavy chain and variable light chain of an anti-NGF antibody, said transgenes being detectably expressed in the mouse by post natal day 90, wherein the mouse has or is predisposed to developing an adult neurodegenerative pathology characterized by a variety of symptoms recited in claim 1.

The scope of anti-NGF antibodies is not limited, such that the scope embraces any antibody that binds NGF.

Cattaneo et al (J. Neurochem. 50(4): 1003-1010, 1988) taught that there were at least two types of antibodies that bound NGF, including those that inhibit NGF activity by inhibiting binding to target cells, and those that do not inhibit NGF activity (see abstract). NGF is known to bind high affinity (TrkA) and low affinity (p75) receptors. Molnar et al (Eur. J. Neurosci. 10: 3127-3140, 1998) taught that the alpha D11 anti-NGF monoclonal antibody (expressed by the mice exemplified in the instant specification) inhibited NGF binding to both TrkA and p75 receptors (see page 3130, paragraph bridging columns 1 and 2). The prior art taught other monoclonal antibodies that inhibited NGF receptor binding (see e.g. Nanduri et al (J. Neurosci. Res. 37(4): 433-

444, 1994). In view of the specification as a whole, the instantly claimed mice derive their phenotype through the action of the alphaD11 monoclonal antibody inhibiting the action of NGF. It follows that antibodies that recognize NGF, but that do not inhibit its activity, will not give the claimed phenotype. The specification discloses no anti-NGF antibodies that inhibit NGF activity but do not inhibit NGF receptor binding. As a result the specificat5ion is enabling only for mice that express anti-NGF antibodies that inhibit NGF binding to its receptors.

Connor et al (J. Neurosci. Meth. 65: 93-99, 1996) taught that neurotrophins, including e.g. BDNF, NT-3, and NGF, are highly conserved structurally, but have diverse functions. See page 93, first full paragraph of introduction. Connor also taught that some antibodies raised against NGF cross react with other neurotrophins under biological conditions, see e.g. abstract and paragraph bridging pages 96 and 97. The instant specification discloses that the alpha D11 monoclonal antibody is specific for an NGF epitope that is not conserved in other neurotrophins, and is therefore NGF-specific and does not cross react with other neurotrophins.

The prior art taught that the production of transgenic animals with desired characteristics is highly unpredictable. The instant invention relies upon expression of an antibody against an endogenous protein e.g. NGF, to approximate the effect of eliminating the expression of that protein. As such, the instant invention is similar to a "knock out" transgenic animal in which a gene of interest has been disrupted. However, at the time of the invention, the phenotype of mice in which expression of targeted genes is reduced was not considered to be predictable. This is apparent from

numerous reports as discussed in the previous actions. See for example, Kappel et al (1992) (knock outs of beta2 microglobulin, interleukin 2, interleukin 4, and CD38 were expected to cause severe immuno-incompetence, but this phenotype was not observed in the actual animals, early developmental lethality was expected for knockouts of src, but homozygous src -/- null animals can survive for at least 5 months, and no detrimental effects were observed in the tissues where src expression is highest), Melton (1994) (mice comprising myoD knockouts possessed muscle and developed normally and had unexpected changes in the expression of myf-5, myf-5 null mice had changes in the expression of myoD), and Moreadith (1997) (HPRT knockouts to generate a model of Lesch-Nyhan syndrome had no readily apparent neurological defect). These teachings, taken together, illustrate the unpredictable nature of knockout mouse phenotypes, and suggest that this is due to the fact that gene interactions are generally poorly understood, as are the potential compensatory actions which are available to the subject animals. As a result the phenotype of a transgenic mouse comprising an antibody that inhibits not only NGF, but other neurotrophins as well, is considered to be highly unpredictable.

In view of the art-recognized unpredictability of transgenic animal phenotypes, the unpredictability associated with transgene expression, and the scope of anti-NGF antibodies embraced by the claims, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 5/30/06 have been fully considered but they do not apply to this new ground of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8, 11-14, and 38-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Cattaneo et al (Society for Neuroscience Abstracts 22 (1-3): 753, 1996) as evidenced by Werth et al (Exp. Neurol. 161:203-211, 2000).

Instant claim 1 is drawn to a transgenic mouse whose genome comprises transgenes encoding a variable heavy chain and a variable light chain of an anti-NGF antibody, wherein the transgenes are expressed by day 90 postnatal, said mouse "having, or being predisposed to the development of, an adult neurodegenerative pathology characterized by the presence of" seven different symptoms including cholinergic deficit. It is unclear from the phrase "adult neurodegenerative pathology characterized by the presence of" whether or not each of the symptoms is required to be present in the claimed mouse, or whether the mouse can have any adult neurodegenerative pathology, so long as that pathology may, in some cases show one

or more of the recited symptoms. This second interpretation is the broadest reasonable interpretation of the claims, and is applied here.

Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of the alpha D11 mouse monoclonal antibody against NGF joined to human constant regions, under the control of a CMV early promoter. Antibody was expressed at 50-100 ng/ml in adult mice. The adult mice show a 30% reduction in neurons of the superior cervical ganglia. This phenotypic characteristic is considered to consonant with a cholinergic deficit, in view of the evidence of Werth. Werth showed that superior cervical ganglion cells deprived of NGF displayed a nicotinic cholinergic current density that was 50% of controls that received NGF. Absent evidence to the contrary, the mice of Cattaneo show the same deficit. In view of the specification as filed, this cholinergic deficit is characteristic of Alzheimer's.

Claims 39-45 are included in this rejection because Cattaneo had to isolate brain tissue in order to determine the loss of superior ganglion cells, and had to isolate blood in order to determine the serum concentration of the antibody. Note that the claims do not require isolation of these tissues, and so claims 41, 42, 44, and 45, drawn to tissues not disclosed as isolated by Cattaneo, are anticipated because the mice of Cattaneo inherently comprise these tissues.

Response to Arguments

Applicant's arguments filed 5/30/06, and the Declaration of Dr. Cattaneo, have been fully considered as they might apply to the ground of rejection set forth above, but

they are unpersuasive. Applicant argues that the claimed mice are different from the mice of Cattaneo (1996). Essentially Applicant, and Dr. Cattaneo in the declaration, argue that the phenotype of the claimed mice is different than the phenotype of the mice of Cattaneo (1996). This is unpersuasive for the reasons set forth in the rejection, i.e. the claims were interpreted broadly to embrace mice that showed only a single one of the recited phenotypic characteristics, not all of them, and the mouse of Cattaneo (1996) is deemed to show a cholinergic deficit due to its loss of superior cervical ganglion cells. For this reason the rejection is considered to be proper.

Previously it was indicated that should Applicant submit evidence under 37 CFR 1.132 that proved that the mice of Cattaneo (1996) did not have the claimed phenotypic characteristics, even though they comprised an identical transgene, this would constitute evidence of the unpredictability of the phenotype of the claimed transgenic mice. In particular, since there is no discernable difference in the structure of the mice, and no guidance as to how to reproducibly make the parental mice of the instant invention instead of the parental mice of Cattaneo (1996), it would appear that the parental strains would have to be deposited under the conditions of 37 C.F.R. 1.801-1.809 in order to enable claims to a mouse made by crossing those specific lines. However, Applicant's response and the Declaration of Dr. Cattaneo, filed 5/30/06 are persuasive regarding the physical and phenotypic distinctions of the mouse of Cattaneo (1996) and the mice of families 1 and 2 disclosed in the instant specification. Further, it would not take undue experimentation for one of skill in the art to reproduce the mice of families 1 and 2 given the guidance in the specification and the state of the art. As

applicant argues in the response, it is common when making transgenic animals to obtain a wide variety of expression levels due to position effects. It would not require undue experimentation to perform crosses between mice with varying levels of heavy and light chain expression in order to arrive at the claimed mice, particularly in view of the guidance in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 14-16, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cattaneo et al (1996) in view of Poul et al (Immunotechnology 1: 189-196, 1995).

The teachings of Cattaneo are described above. Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of mouse monoclonal antibody against NGF joined to human constant regions, under the control of a CMV early promoter. Antibody was expressed at 50-100 ng/ml in adult mice. The mice show a 30% reduction in neurons of the superior cervical ganglia. In view of the specification as filed, this deficit is characteristic of Alzheimer's.

Cattaneo was silent as to what human heavy and light chain variable regions were used to make the chimeric antibody transgenes.

Poul taught a general expression vector for producing humanized antibodies. The vector contained human light chain kappa constant region sequences, and human heavy chain gamma 1 sequences organized to allow insertion of mouse variable region sequences of choice in operable linkage with the human constant regions. Thus it was routine in the art at the time of the invention to use human light chain kappa and heavy chain gamma regions in the construction of humanized monoclonal antibodies, and so it would have been obvious to one of ordinary skill in the art at the time of the invention to have used these constant regions in the constructs of Cattaneo.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cattaneo et al (1996) in view of Hogan et al (In *Manipulating the Mouse Embryo,* Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pg 81, 1986).

The teachings of Cattaneo are described above. Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of mouse monoclonal antibody against NGF joined to human constant regions, under the control of a CMV early promoter. Antibody was expressed at 50-100 ng/ml in adult mice. The mice show a 30% reduction in neurons of the superior cervical ganglia. In view of the specification as filed, this deficit is characteristic of Alzheimer's.

Hogan taught that there was a variety of mouse hybrid zygotes that were suitable for the formation of transgenic mice, including hybrids of C57BL/6J and SJL mice, i.e. B6SJL zygotes. See page 81.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the B6SJL hybrid zygotes of Hogan to make the transgenic mice of Cattaneo because Hogan indicated that these zygotes were among several types of zygotes routinely used for the purpose of making transgenic animals. The selection of a particular zygote were among several suitable types is merely a matter of design choice and, absent case specific indications to the contrary, the zygotes available for use can be viewed as art-recognized equivalents.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 5/30/06, and the Declaration of Dr. Cattaneo, have been fully considered as they might apply to the ground of rejection set forth above, but they are unpersuasive for the reasons set forth under 35 USC 102 rejections, above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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